

AUTOIMMUNITY CENTERS OF EXCELLENCE

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P.T.

National Institute of Allergy and Infectious Diseases
National Institute of Diabetes and Digestive and Kidney Diseases
National Institute of Arthritis and Musculoskeletal and Skin Diseases
Office of Research on Women's Health

Letter of Intent Receipt Date: December 8, 1998

Application Receipt Date: January 8, 1999

APPLICATIONS IN RESPONSE TO THIS REQUEST FOR APPLICATIONS (RFA) MUST BE PREPARED USING SPECIFIC INSTRUCTIONS IN THE NIAID BROCHURE ENTITLED "INSTRUCTIONS FOR APPLICATIONS FOR MULTI-PROJECT AWARDS" (September 1997).

PURPOSE

The National Institute of Allergy and Infectious Diseases (NIAID), National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), and the Office of Research on Women's Health (ORWH) invite applications for Autoimmunity Centers of Excellence. The purpose of this cooperative research program is to support integrated basic, pre-clinical and clinical research centers to: conduct single site and multi-site cooperative clinical trials and studies of mechanisms of action of tolerance induction and new immune modulation interventions in multiple autoimmune diseases; accelerate early translation of basic findings into clinical application; facilitate the utilization of clinical materials for basic research studies; enhance the exchange of information between basic scientists and clinicians and among various specialists involved in treating autoimmune diseases; and establish a collaborative approach to clinical and basic research among multiple institutions in various geographic areas. Each Center will include: 1) a clinical component, incorporating multiple clinical specialists to conduct trials and clinical studies of new immunotherapies for autoimmune diseases in cooperation with other Center clinical components, and 2) two or more multidisciplinary, interactive basic and/or pre-clinical research components, focused on

elucidation of the basic mechanisms of autoimmunity, self tolerance and/or immune modulation. The basic and clinical components of all Centers will work cooperatively to select, design, and perform the clinical trials/studies and the adjunct basic mechanistic studies. All applicants must comply with the stipulations outlined in the section of this RFA entitled "SPECIAL REQUIREMENTS."

HEALTHY PEOPLE 2000

The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2000," a PHS-led national activity for setting priority areas. This RFA, Autoimmunity Centers of Excellence, is related to the priority area of diabetes and chronic disabling conditions. Potential applicants may obtain a copy of "Healthy People 2000" (Full Report: Stock No. 017-001-00474-0 or Summary Report: Stock No. 017-001-00473-1) through the Superintendent of Documents, Government Printing Office, Washington, DC 20402-9325 (telephone 202-512-1800).

ELIGIBILITY REQUIREMENTS

Research grant applications may be submitted by domestic for-profit and non-profit organizations, public and private institutions, such as universities, colleges, hospitals, laboratories, units of State and local governments, and eligible agencies of the Federal government. Foreign organizations are not eligible to apply. Racial/ethnic minority individuals, women, and persons with disabilities are encouraged to apply as Principal Investigators.

MECHANISM OF SUPPORT

The administrative and funding mechanism to be used to undertake this program will be the Multiproject Cooperative Agreement (U19), an "assistance" mechanism, rather than an "acquisition" mechanism. Under the cooperative agreement, the NIH purpose is to support and/or stimulate the recipient's activity by involvement in and otherwise working jointly with the award recipient in a partner role, but it is not to assume direction, prime responsibility, or a dominant role in the activity. Essential elements of the multiproject cooperative agreement mechanism also include: (1) a minimum of three interrelated individual research projects organized around a central theme; (2) collaborative efforts and interaction among independent projects and their investigators to achieve a common goal; (3) a single Principal Investigator who will be scientifically and administratively responsible for the group effort; (4) a single applicant institution that will be legally and financially responsible for the use and

disposition of funds awarded; and (5) support provided, as necessary, for "Core" resources or facilities, each of which is expected to be utilized by at least two research projects in order to facilitate the research effort. Details of the responsibilities, relationships and governance of a study funded under a cooperative agreement are discussed later in this document under the section "Terms and Conditions of Award."

The total project period for an application submitted in response to this RFA may not exceed five years. At present, the NIAID is administratively limiting the duration of U19 cooperative agreements to four year; this administrative limitation may change in the future.

FUNDS AVAILABLE

The estimated total funds (direct and indirect) available for the first year of support for this RFA will be \$2.9 million: \$2.25 million from NIAID, \$300,000 from the Office of Research on Women's Health, NIH, \$250,000 from NIDDK, and \$100,000 from NIAMS. In fiscal year 1999, the NIAID plans to make approximately three awards under this RFA. Applicants requesting in excess of \$750,000 in total (direct and indirect) first-year costs must obtain approval from the program contact, listed under INQUIRIES, prior to submission. This level of support is dependent on the receipt of a sufficient number of applications of high scientific merit. NIAID will also fund by a separate solicitation a Data and Operations Center to support the Autoimmunity Centers of Excellence.

The usual PHS policies governing grants administration and management will apply. Although this program is provided for in the financial plans of the NIAID, awards pursuant to this RFA are contingent upon the availability of funds for this purpose. Funding beyond the first and subsequent years of the grant will be contingent upon satisfactory progress during the preceding years and availability of funds.

At this time, the NIAID has not determined whether or how this solicitation will be continued beyond the present RFA.

RESEARCH OBJECTIVES

Background

Autoimmune disease results from direction of an immune response towards the body's own tissues. The most common of these diseases include systemic lupus erythematosus, multiple

sclerosis, type 1 diabetes mellitus, and rheumatoid arthritis. However, the immune response toward self can affect any organ or organ system, resulting in a wide variety of autoimmune diseases, including autoimmune myositis, thyroid disease, oophoritis and orchitis, hepatitis, hemolytic anemia, pemphigus, inflammatory bowel disease, and alopecia. Many of these autoimmune diseases by themselves are considered orphan diseases, but in toto autoimmune diseases disproportionately afflict millions of women in this country. The costs of these diseases are enormous, including hospitalizations, outpatient visits, lost productivity, and decreased quality of life for patients and their families.

The underlying immune mechanisms of these multiple diseases may be overlapping. Specifically, self-reactive T cells play an important role in the immune responses leading to many of these clinically divergent diseases. The presence, number, activity, and specificity of these self-reactive cells are regulated by complex processes involving multiple molecules and mechanisms. These include the binding and presentation of antigen by the molecules of the major histocompatibility complex (MHC), the number and affinity of specific T cell receptors for these complexes, the presence of co-stimulatory molecules, including the B-7 and CD40 families, the activity of regulatory T cells, both T helper and T cytotoxic cells, the presence and pattern of extracellular mediators including cytokines, lymphokines, and chemokines, and the intracellular pathways leading to apoptosis or cell death. Strategies to interrupt the immune response at any of these sites could prevent or down regulate the self-reactive response leading to autoimmune disease. In fact, agents which block co-stimulatory signals (anti-CD40L, CTLA4-Ig) or cytokines (anti-TNF-alpha, TNFR:Fc, IL-1Ra), interrupt or alter binding of antigen to MHC (antigen peptides, MHC peptides, peptide oligomers), or modulate the appearance and activity of regulatory cells (various cytokines and anti-cytokines) are now being evaluated for treatment of multiple autoimmune diseases. Other approaches are likely to be discovered in the next few years. Clinical evaluation of new immune interventions in various diseases has often been performed without basic mechanistic studies to define the actions of the experimental agents. Closer interaction between clinicians and basic scientists should accelerate clinical testing of new approaches to tolerance induction and immune modulation and enhance understanding of their underlying mechanisms of action.

Since the affected organ systems vary in different diseases, autoimmune diseases are treated by multiple clinical specialists. Thus, multiple sclerosis is treated by neurologists, type 1 diabetes, Graves' disease, and Hashimoto's thyroiditis by endocrinologists, systemic lupus erythematosus, rheumatoid arthritis, and scleroderma by rheumatologists, idiopathic thrombocytopenia purpura by hematologists, and inflammatory bowel disease by gastroenterologists; many diseases are treated by multiple specialists. Because all these diseases will be increasingly approached with

immunologic interventions, a cooperative group with the capability to evaluate a new agent in any of a number of diseases offers considerable advantages. Increased interaction of clinical specialists in planning, performance, and evaluation of trials/studies should lead to a more coordinated approach to development of new immune-based therapies for all autoimmune diseases.

Research Objectives and Scope

The major goal of this program is to support an integrated basic and clinical research program focused on tolerance induction and immune modulation to prevent or treat autoimmune disease. The close interaction between basic researchers and clinicians will accelerate the translation of basic advances to the clinic and the utilization of patient materials for basic research.

NIAID is seeking multidisciplinary centers that emphasize new ideas, novel approaches, and state of the art technology to increase our understanding of the basic mechanisms of autoimmunity and self tolerance and the translation of that knowledge to design and evaluate clinical interventions to prevent or treat autoimmune diseases. The clinical components of the Autoimmunity Centers of Excellence will perform pilot or exploratory clinical trials or clinical studies, hereafter designated clinical trials/studies, in patients with autoimmune disease(s) to test, evaluate, develop, or determine mechanism of action of agents or interventions to prevent or treat autoimmune disease by induction of tolerance or immune modulation. While industry has supported some translational activities, industry-supported trials have generally not focused on questions about the basic mechanisms of action of these agents. Collaboration of the Autoimmunity Centers of Excellence with industry in performance of clinical trials/studies and adjunct basic mechanistic studies is encouraged.

Specific areas of interest include, but are not limited to:

- o clinical trials of tolerogenic and immunomodulatory approaches and agents to treat and prevent autoimmune disease, including co-stimulatory blockade, such as anti-CD40 ligand antibody and CTLA4-Ig; cytokines and anti-cytokine molecules, such as anti-TNF, IL-4, and IL-12; and peptide ligands, such as MHC peptides, antigen-specific peptides, or peptide oligomers;
- o stem cell and bone marrow transplantation for treatment of autoimmune disease; determination of course of development of tolerance and/or immunity, the cells that are necessary for tolerance induction, and the role of chimerism;

- o relationship of response to therapy and various parameters: stage of disease, subsets of disease (i.e., relapsing vs. chronic progressive multiple sclerosis), patient characteristics including race, ethnic background, and genetic background, route of administration of agents;
- o development of new clinically useful agents to modulate the immune response and modification of currently available agents to enhance agonist or antagonist activity, to enhance efficacious activity, and/or eliminate adverse effects;
- o determination of the mechanism of action of agents utilized: the role of cytokines, regulatory T cells, accessory cells (including macrophages, NK cells, dendritic cells, and B cells), shifts in T cell subset response, T cell anergy, T cell deletion, or induction of cell death pathways;
- o mechanisms responsible for tolerance initiation, maintenance, or loss; and
- o basic hypothesis driven research into mechanisms of self tolerance, the pathogenesis of human autoimmune disease and/or its modulation.

SPECIAL REQUIREMENTS

1. Clinical Component

Each Autoimmunity Center of Excellence must include a clinical research component, which encompasses participation by multiple clinical specialists, who have access to patient populations in which to conduct clinical trials/studies in autoimmune diseases. This component must include a minimum of three clinical specialties and demonstrate the ability to perform clinical trials/studies in at least three different autoimmune diseases. The clinical component may represent a single institution or a consortium of institutions. Diseases amenable to clinical intervention and of interest to the NIAID include, but are not limited to: systemic lupus erythematosus, multiple sclerosis, rheumatoid arthritis, type 1 diabetes mellitus, idiopathic thrombocytopenia purpura, inflammatory bowel disease, and scleroderma. Specialists that could participate in the clinical component include, but are not limited to: endocrinologists, neurologists, rheumatologists, gastroenterologists, and hematologists. The multiple specialists in the clinical component must be willing and able to work collaboratively and cooperatively, both within their Center and with clinical and basic components of other Centers to facilitate clinical and adjunct basic studies. The application should include written letters of commitment to this principal. Applications proposing clinical components that do not meet the above criteria concerning the number of clinical

specialties represented and available disease populations will be judged non-responsive and returned to the applicant without review.

The application for the clinical component should describe the populations of patients available for utilization in clinical trials/studies, and demonstrate the ability to perform clinical trials/studies, including the ability to recruit and retain subjects for at least three different autoimmune diseases. The application should include two proposed clinical trial/study protocols for immune interventions for autoimmune diseases. These protocols should include the rationale for the agent(s) and disease(s) selected, patient population, study design, and primary and secondary outcome measures. These two protocols may utilize the same or different agents, but must intervene on different autoimmune diseases. Award of a Center does not imply that the proposed protocols will be implemented. Since the clinical trials/studies that are ultimately undertaken by the Centers will be selected by the Steering Committee (see below), the trials/studies selected for implementation may not be identical to any single protocol submitted in response to this RFA. Funding for clinical components will be contingent upon participation in approved clinical studies or trials.

In addition to the two proposed clinical trials/studies submitted with the application, proposals for adjunct basic studies related to these clinical trials/studies should be included in the application. The submitting Center's basic components do not necessarily need to include the expertise to perform these studies, however, the studies must be feasible, i.e., the techniques must be established.

2. Basic Components

Each Autoimmunity Center of Excellence must include two or more basic research components. The basic components must be multi-disciplinary, interactive basic or pre-clinical research projects focused on elucidation of the basic mechanisms and pathogenesis of autoimmunity, self tolerance, and/or immune modulation. In addition to the proposed basic research project, each basic component must demonstrate interest and capability for carrying out adjunct basic studies related to clinical trials/studies in the context of an overall Centers' program; work cooperatively with basic and clinical components from their and other Centers; work with clinicians in development of clinical trials/studies; and attend biannual Centers' meetings. These basic components may utilize animal models for their studies, but must also incorporate basic research in humans.

Centers Network Organization

Steering Committee

A Steering Committee will be established to serve as the main governing body of the cooperative network. At a minimum, the Steering Committee will be composed of the NIAID Autoimmunity Research Coordinator and two representatives from each of the Centers: one Clinical Research Representative and one Basic Research Representative. The Clinical Research Representative is the person responsible for the overall management of the clinical research component, including: coordination of the participating Center specialists, whether within a single institution or a consortium of institutions; design and submission of proposed protocols for clinical trials/studies; and implementation, monitoring, and data submission and analysis of clinical trials/studies. This person must be a physician with substantial training and experience in 1) clinical management of one or multiple autoimmune diseases, 2) clinical immunology, and 3) the design, implementation and evaluation of clinical trials. The Basic Research Representative is the person responsible for coordination of the Center's basic research scientists, whether within a single institution or a consortium of institutions, in: development of proposed clinical trials/studies and adjunct basic studies in cooperation with clinicians, conduct of the basic studies in conjunction with ongoing clinical trials/studies; and collaboration and sharing of basic resources and reagents within a Center and with other Centers. The collaboration of clinicians and/or basic scientists from different Centers is highly encouraged based on shared interests and complementary talents. Designation of the Clinical Research Representative and the Basic Research Representative is the responsibility of the Center Principal Investigator, who may serve as either representative, but not both. The Chairperson of the Steering Committee will be selected by the Steering Committee from among the non-Federal members during one of the early meetings of the Committee to be convened by the NIAID Autoimmunity Research Coordinator. All major scientific decisions will be determined by the Steering Committee, with each Clinical Research Representative, Basic Research Representative, and the NIAID Autoimmunity Research Coordinator having one vote. The Committee will meet at least three times during the first 12 months of the program and at least semi-annually thereafter.

The Steering Committee will have responsibility for facilitating the conduct of clinical trials/studies and basic research related to these trials/studies, promoting trans-Center collaboration among and between clinical and basic components, analyzing and interpreting Center-wide study data, and establishing procedures for reporting results of Center trials/studies. Proposed protocols for clinical trials/studies to be performed by a single Center or groups of Centers will be submitted to the Steering Committee for review and evaluation. Protocols to be implemented will be selected by the Steering Committee in accordance with criteria and procedures established by the Steering Committee. Timely review and evaluation are expected. After approval, those clinical

investigators participating in the trial/study in collaboration with investigators from the basic components who will be performing adjunct basic mechanistic studies will develop detailed protocols. As needed, the Steering Committee may establish subcommittees for special purposes. It is expected that most of the work of the Steering Committee will be performed in these subcommittees. Clinical trials/studies will proceed into the implementation stage only with the concurrence of the Steering Committee and the NIAID Autoimmunity Research Coordinator. Each Basic and Clinical Research Representative will be expected to actively participate in all other Steering Committee activities.

b. Data, Safety and Quality Monitoring Board

The NIAID will appoint an independent Data, Safety and Quality Monitoring Board to review the endpoint and safety data for all trials/studies on an ongoing basis, but at least twice a year, and report directly to the NIAID Autoimmunity Research Coordinator. Protocols and data collection and quality assurance procedures will be reviewed by this Board in an advisory capacity. This Board will be funded separately from the Centers.

c. Biannual Centers Meetings

A meeting of the Principal Investigators of each Clinical and Basic research project from all of the Centers (usually 3 investigators/Center) will be held biannually at a site designated by the NIAID (usually Washington, DC). Each of the Principal Investigators will present significant findings and report on progress, review the focus and plan of the Centers' program, and establish and strengthen collaborations among the Centers. It is expected that meetings of the Steering Committee and other Centers committees will occur in conjunction with this meeting. Travel funds for these meetings should be included in the budget of the individual Centers.

Additional Application Requirements

To promote the development of an interactive integrated network, a minimum number of issues need to be addressed in the applications, as outlined below.

a. Intra- and Inter-Institutional Arrangements

Single institutions or consortia of institutions may submit applications.

However, the application must identify a single applicant organization that will be legally and financially responsible and accountable for the use and disposition of funds awarded to the other

institutions. The development of Centers, which include multiple institutions and geographic areas, is encouraged when such an institutional arrangement provides the most appropriate mixture of clinical and basic science components. Evidence that the components can work together effectively must be provided in all applications regardless of whether the applicant is a single institution or a consortium of institutions.

b. Cooperative and Collaborative Responsibilities

Each clinical and basic component of each Center must be willing to work cooperatively and collaboratively both within their Center and with other Centers. The application must indicate commitment/willingness to the collaborative organization, steering committee, and participation of NIAID staff as described in the "Terms and Conditions." The Steering Committee as defined in section entitled "Steering Committee" will be the main governing body of the Centers network and will have responsibility for establishing procedures for the selection of clinical trials/studies and adjunct basic studies to be performed; developing procedures for prioritization of use of samples from patients for basic studies; implementing clear, inclusive, and effective communication among the components of all Centers; establishing procedures for the monitoring of performance and progress of the clinical trials/studies, including accrual, timely submission and quality of data and samples, and conscientious observance of protocol requirements; and instituting procedures for data collection, management, quality control, and reporting results of clinical trials/studies.

c. Budgets

All costs requested for the proposed studies must be included in the application. Requested budgets should include: 1) travel for three one-day Steering Committee meetings during the first 12 months of the study and semiannual Steering Committee meetings thereafter for the Clinical and Basic Research Representatives of each Center; and 2) travel for the Principal Investigator of the Center components to a two-day biannual meeting (usually in Washington, DC area), beginning in the second year.

Funding for clinical components will be contingent upon participation in approved clinical studies or trials/studies.

TERMS AND CONDITIONS OF AWARD

The following terms and conditions will be incorporated into the award statement and provided to the Principal Investigator as well as the institutional official at the time of award.

These special Terms of Award are in addition to, and not in lieu of, otherwise applicable OMB administrative guidelines, HHS Grant Administration Regulations at 45 CFR part 74 and 92, and other HHS, PHS, and NIH Grant Administration policy statements. The administrative and funding instrument used for this program is the multiproject cooperative agreement (U19), an "assistance" mechanism (rather than an "acquisition" mechanism), in which substantial NIH scientific and/or programmatic involvement with the awardee is anticipated during the performance of the activity. Under the cooperative agreement, the NIH purpose is to support and/or stimulate the recipient's activity by involvement in and otherwise working jointly with the award recipient in a partner role, but it is not to assume direction, prime responsibility, or a dominant role in the activity. Consistent with this concept, the dominant role and prime responsibility for the activity resides with the awardees for the project as a whole, although specific tasks and activities in carrying out the research will be shared among the awardees and the NIAID Autoimmunity Research Coordinator.

1. Awardee Rights and Responsibilities

Awardees will have primary responsibility for defining the details of the project within the guidelines of the RFA and for performing the scientific activity, and agree to accept close coordination, cooperation, and participation of the NIAID staff in all aspects of the scientific and technical management of the project. Specifically, awardees have primary responsibility as described below.

Steering Committee Membership and Meeting Attendance

Each Center Principal Investigator will designate a Clinical Research Representative and a Basic Research Representative as defined under "Steering Committee" to serve as voting members of the Steering Committee and participate in all Committee decisions. Each Clinical and Basic Research Representative will be responsible for attending all Steering Committee meetings, including not less than three during the first 12 months of the program and two per year thereafter. The Steering Committee shall be responsible for determining the frequency of meetings and scheduling the time and location. Each Clinical and Basic Research Representative will be expected to participate in all other Steering Committee activities, including, but not limited to, conference calls and special subcommittees as may be necessary. The Steering committee will establish the procedures for the function of the Centers network, as outlined in section "Steering Committee."

Data Coordination and Management

The NIAID will be responsible for ensuring the provision of centralized data management and coordination assistance, including analysis support. This Data Management service will be funded separately from the Centers. Under the direction of the Steering Committee, the NIAID will provide technical assistance and data management services to the Autoimmunity Centers of Excellence with respect to quality control, uniformity of data collection, management of the collective data base, and data analysis.

Each awardee will be responsible for providing the NIAID with all primary study data for management, quality control and analysis, using procedures and standards determined by the Steering Committee. All data will be available to all awardees. Specific analysis to be performed by NIAID will be directed by the Steering Committee or its designee. The awardees will retain custody of and have primary rights to all data developed under these awards, subject to Government rights of access consistent with HHS and NIH policies.

Publication and Presentation of Study Findings

Early publication of major findings is encouraged. Publications and oral presentations of work performed under this agreement will require appropriate acknowledgment of the Autoimmunity Centers of Excellence and NIAID support. Analyses to be performed using collective data from multiple centers will be determined by the Steering Committee. Centers wishing to perform analysis of local data or of single site studies should inform the Steering Committee prior to initiation to avoid duplication. The Steering Committee will establish the procedures and criteria for presentation and publication of data developed within the Centers network.

Federally Mandated Regulatory Requirements

Each institution participating in the Clinical component of an Autoimmunity Center of Excellence is required to meet DHHS regulations for the protection of human subjects and FDA requirements for the conduct of research using investigational agents. At a minimum, these include:

- o methods for assuring that each institution at which Autoimmunity Centers of Excellence investigators are conducting clinical studies has a current, approved assurance on file with the Office of Protection from Research Risks (OPRR); that study protocols are reviewed and approved by the responsible Institutional Review Board (IRB) prior to patient entry; that active protocols are reviewed at least annually by the IRB, and that amendments are approved by the IRB.

- o methods for assuring or documenting that each patient, or patient's parent/legal guardian, gives fully informed consent to participation in a research protocol prior to the initiation of the experimental intervention.

2. NIAID Staff Responsibilities

NIAID staff assistance will be provided by an NIAID Autoimmunity Research Coordinator, who will have substantial scientific/programmatic involvement during the conduct of this activity through technical assistance, advice and coordination above and beyond normal program stewardship for grants, as described below.

Steering Committee Membership and Meeting Attendance

The NIAID Autoimmunity Research Coordinator will serve as a voting member of the Steering Committee, will attend all Steering Committee meetings, and will participate in other Committee activities, including, but not limited to, conference calls, subcommittees, and special committees.

Clinical Trials Protocol Development

As a member of the Steering Committee, the NIAID Autoimmunity Research Coordinator will serve as a resource with respect to the design of protocols.

Study Materials

The NIAID may negotiate with companies interested in participating in trials or studies. The NIAID may facilitate the appropriate approvals (when necessary) from the Food and Drug Administration with respect to the use of investigational drugs.

Monitoring Performance

The NIAID Autoimmunity Research Coordinator will provide assistance to the Steering Committee in the development of procedures for monitoring the performance of the clinical trials/studies. This includes participation in periodic on-site monitoring with respect to compliance with protocol specifications, quality control and accuracy of data recording, and accrual.

Clinical Data Coordination and Management

The NIAID will be responsible for ensuring the provision of centralized data management and coordination assistance, including analysis support. Under the direction of the Steering Committee, the NIAID will provide technical assistance and data management services to the Autoimmunity Centers of Excellence with respect to quality control, uniformity of data collection, management of the collective data base, and data analysis.

The Government, via the NIAID Autoimmunity Research Coordinator, will have access to data generated under this Cooperative Agreement and may periodically review the data and progress reports. Information obtained from the data may be used by NIAID staff for the preparation of internal reports on the activities of the clinical trials/studies. However, awardees will retain custody of and have primary rights to all data developed under these awards.

Publication and Presentation of Clinical Trials/Studies Findings

The NIAID Autoimmunity Research Coordinator may contribute, through review, comment, analysis, and/or co-authorship, to reporting results of the clinical studies and trials/studies to the investigator community and other interested scientific and lay organizations. Co-authorship by the NIAID Autoimmunity Research Coordinator will be subject to approval in accordance with the NIH policies regarding staff authorship of publications resulting from extramural awards.

Organizational Changes

Certain organizational changes require the prior written approval of the NIAID Autoimmunity Research Coordinator. These changes include the addition/substitution/removal of a principal investigator, clinical component, basic component, or member of an affiliated clinical group associated with the Centers network. A change in the designated principal investigator, or in any key personnel identified in the application, must have the prior written approval of the NIAID Grants Management Specialist in consultation with the NIAID Autoimmunity Research Coordinator.

Program Review

The NIAID Autoimmunity Research Coordinator will review the progress of each Autoimmunity Center through consideration of the annual reports, site visits, patient logs, etc. This review may include, but is not limited to, participation in and compliance with clinical trials/studies protocols, uniform data collection and timely reporting of data, and participation in collaborative basic studies.

Collaborative Responsibilities

Each clinical and basic component of each Center must be willing to work cooperatively and collaboratively both within their Center and with other Centers. The application must indicate commitment/willingness to the collaborative organization, steering committee, and participation of NIAID staff as described in the "Terms and Conditions of Award: NIAID Staff Responsibilities."

The Steering Committee as defined below will be the main governing body of the Centers network and will have responsibility for establishing procedures for the selection of clinical trials/studies and adjunct basic studies to be performed; developing procedures for prioritization of use of samples from patients for basic studies; implementing clear, inclusive, and effective communication among the components of all Centers; establishing procedures for the monitoring of performance and progress of the clinical trials/studies, including accrual, timely submission and quality of data and samples, and conscientious observance of protocol requirements; and instituting procedures for data collection, management, quality control, and reporting results of clinical trials/studies.

a. Steering Committee

A Steering Committee will be established to serve as the main governing body of the cooperative network. At a minimum, the Steering Committee will be composed of the NIAID Autoimmunity Research Coordinator and two representatives from each of the Centers: one Clinical Research Representative and one Basic Research Representative. The Clinical Research Representative is the person responsible for the overall management of the clinical research component, including: coordination of the participating Center specialists, whether within a single institution or a consortium of institutions; design and submission of proposed protocols for clinical trials/studies; and implementation, monitoring, and data submission and analysis of clinical trials/studies. This person must be a physician with substantial training and experience in 1) clinical management of one or multiple autoimmune diseases, 2) clinical immunology, and 3) the design, implementation and evaluation of clinical trials. The Basic Research Representative is the person responsible for coordination of the Center's basic research scientists, whether within a single institution or a consortium of institutions, in: development of proposed clinical trials/studies and adjunct basic studies in cooperation with clinicians, conduct of the basic studies in conjunction with ongoing clinical trials/studies; and collaboration and sharing of basic resources and reagents within a Center and with other Centers. The collaboration of clinicians and/or basic scientists from different Centers is highly encouraged based on shared interests and complementary talents. Designation of the Clinical Research Representative and the Basic Research Representative is the responsibility of the Center Principal Investigator, who may serve

as either representative, but not both. The Chairperson of the Steering Committee will be selected by the Steering Committee from among the non-Federal members during one of the early meetings of the Committee to be convened by the NIAID Autoimmunity Research Coordinator. All major scientific decisions will be determined by the Steering Committee, with each Clinical Research Representative, Basic Research Representative, and the NIAID Autoimmunity Research Coordinator having one vote. The Committee will meet at least three times during the first 12 months of the program and at least semi-annually thereafter.

The Steering Committee will have responsibility for facilitating the conduct of clinical trials/studies and basic research related to these trials/studies, promoting trans-Center collaboration among and between clinical and basic components, analyzing and interpreting Center-wide study data, and establishing procedures for reporting results of Center trials/studies. Proposed protocols for clinical trials/studies to be performed by a single Center or groups of Centers will be submitted to the Steering Committee for review and evaluation. Protocols to be implemented will be selected by the Steering Committee in accordance with criteria and procedures established by the Steering Committee. Timely review and evaluation are expected. After approval, those clinical investigators participating in the trial/study in collaboration with investigators from the basic components who will be performing adjunct basic mechanistic studies will develop detailed protocols. As needed, the Steering Committee may establish subcommittees for special purposes. It is expected that most of the work of the Steering Committee will be performed in these subcommittees. Clinical trials/studies will proceed into the implementation stage only with the concurrence of the Steering Committee and the NIAID Autoimmunity Research Coordinator. Each Basic and Clinical Research Representative will be expected to actively participate in all other Steering Committee activities.

4. Arbitration

Any disagreement that may arise on scientific or programmatic matters (within the scope of the award) between award recipients and the NIAID may be brought to arbitration. An arbitration panel will be formed to review any scientific or programmatic issue that is significantly restricting progress. This panel will be composed of three members -- one selected by the Steering Committee or by the individual awardee in the event of an individual disagreement, a second member selected by the NIAID, and a third member with expertise in the relevant area and selected by the two prior members. While the decisions of the Arbitration Panel are binding, these special arbitration procedures will in no way affect the awardee's right to appeal an adverse action in accordance with PHS regulations at 42 CFR Part 50, subpart D, and HHS regulations at 45 CFR Part 16.

Cooperative agreements are subject to the administrative requirements outlined in OMB circulars A-102 and A-110. All pertinent HHS, PHS, and NIH grant regulations, policies and procedures, with particular emphasis on PHS regulations at 42 CFR Part 52 and HHS regulations at 45 CFR Part 74, are applicable. These special terms and conditions pertaining to the scope and nature of the interaction between the NIAID and the investigators will be incorporated in the Notice of Grant Award. However, these terms will be in addition to, not in lieu of, the customary programmatic and financial negotiations that occur in the administration of cooperative agreements.

INCLUSION OF WOMEN AND MINORITIES IN RESEARCH INVOLVING HUMAN SUBJECTS

It is the policy of the NIH that women and members of minority groups and their subpopulations must be included in all NIH supported biomedical and behavioral research projects involving human subjects, unless a clear and compelling rationale and justification are provided that inclusion is inappropriate with respect to the health of the subjects of the purpose of the research. This policy results from the NIH Revitalization Act of 1993 (Section 492B of Public Law 103-43). All investigators proposing research involving human subjects should read the "NIH Guidelines for Inclusion of Women and Minorities as Subjects in Clinical Research", which have been published in the Federal Register of March 28, 1994 (FR 59 14508-14513) and the NIH Guide for Grants and Contracts, Vol. 23, No. 11, March 18, 1994.

INCLUSION OF CHILDREN AS PARTICIPANTS IN RESEARCH INVOLVING HUMAN SUBJECTS

It is the policy of NIH that children (i.e., individuals under the age of 21) must be included in all human subjects research, conducted or supported by the NIH, unless there are scientific and ethical reasons not to include them. This policy applies to all initial (Type 1) applications submitted for receipt dates after October 1, 1998. All investigators proposing research involving human subjects should read the "NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects" that was published in the NIH Guide for Grants and Contracts, March 6, 1998, and is available at the following URL address:

<http://grants.nih.gov/grants/guide/notice-files/not98-024.html>

LETTER OF INTENT

Prospective applicants are asked to submit, by December 8, 1998, a letter of intent that includes a descriptive title of the overall proposed research, the name, address and telephone number of the Principal Investigator, and the number and title of this RFA. Although the letter of intent is not

required, is not binding, does not commit the sender to submit an application, and does not enter into the review of subsequent applications, the information that it contains allows NIAID staff to estimate the potential review workload and to avoid conflict of interest in the review. The letter of intent is to be sent to Dr. Kevin Callahan at the address listed under INQUIRIES.

APPLICATION PROCEDURES

Applications are to be submitted on the standard research grant application form PHS 398 (rev. 5/95). Application kits are available at most institutional offices of sponsored research and may be obtained from the Division of Extramural Outreach and Information Resources, National Institutes of Health, 6701 Rockledge Drive, MSC 7910, Bethesda, MD 20892-7910, telephone (301) 435-0714, email: GrantsInfo@nih.gov

Applicants for U19 cooperative agreements must follow special application guidelines in the NIAID Brochure entitled "Instructions for Applications for Multi-Project Awards" (Sept 1997); this brochure is available via the WWW at: <http://www.niaid.nih.gov/ncn/tools/multibron.htm>. This brochure presents specific instructions for sections of the PHS 398 (rev. 5/95) application form that must be completed differently than usual.

The RFA label available in the PHS 398 (rev. 5/95) kit must be affixed to the bottom of the face page of the application. Failure to use this label could result in delayed processing of the application such that may not reach the review committee in time for review. In addition, the RFA title (AUTOIMMUNITY CENTERS OF EXCELLENCE) and number (AI-98-010) must be typed on line 2 on the face page of the application form and the "YES" box must be marked.

Submit a signed, typewritten original of the application, including the checklist, and three signed, exact, single-sided photocopies, in one package to:

CENTER FOR SCIENTIFIC REVIEW
NATIONAL INSTITUTES OF HEALTH
6701 ROCKLEDGE DRIVE, ROOM 1040 - MSC 7710
BETHESDA, MD 20892-7710
BETHESDA, MD 20817 (for express/courier service)

At the time of submission, two additional exact copies of the grant application and all five sets of any appendix material must be sent to Dr. Kevin Callahan at the address listed under INQUIRIES.

Applications must be received by January 8, 1999. Applications that are not received as a single package on the receipt date or that do not conform to the instructions contained in PHS 398 (rev. 5/95) application kit (as modified in, and superseded by, the NIAID brochure entitled, "Instructions for Applications for Multi-Project Awards"), will be judged non-responsive and will be returned to the applicant. It is highly recommended that the appropriate Institute program contact be consulted before submitting the letter of intent and during the early stages of preparation of the application. (See program contacts listed under INQUIRIES).

Applicants from institutions that have a General Clinical Research Center (GCRC) funded by the NIH National Center for Research Resources may wish to identify the GCRC as a resource for conducting the proposed research. If so, a letter of agreement from either the GCRC program director or principal investigator could be included with the application.

Concurrent submission of an R01 and a Component Project of a Multi-project Application:
Current NIH policy permits a component research project of a multi-project grant application to be concurrently submitted as a traditional individual research project (R01) application. If, following review, both the multi-project application and the R01 application are found to be in the fundable range, the investigator must relinquish the R01 and will not have the option to withdraw from the multi-project grant. This is an NIH policy intended to preserve the scientific integrity of a multi-project grant, which may be seriously compromised if a strong component project(s) is removed from the program.

Investigators wishing to participate in a multi-project grant must be aware of this policy before making a commitment to the Principal Investigator and awarding institution.

REVIEW CONSIDERATIONS

Review Procedures

Upon receipt, applications will be reviewed for completeness by the Center for Scientific Review (CSR) and for responsiveness by NIAID staff. Incomplete and/or non-responsive applications will be returned to the applicant without further consideration. Applications that are complete and responsive to the RFA will be evaluated for scientific and technical merit by an appropriate peer review group convened by the NIAID in accordance with the review criteria stated below. As part of the initial merit review, a process may be used by the initial review group in which applications will be determined to be competitive or non-competitive based on their scientific merit relative to other applications received in response to the RFA. Applications judged to be competitive will be

discussed and be assigned a priority score. Applications determined to be non-competitive will be withdrawn from further consideration and the Principal Investigator and the official signing for the applicant organization will be notified. The second level of review will be provided by the National Advisory Allergy and Infectious Diseases Council and the National Diabetes and Digestive and Kidney Diseases Advisory Council.

Review Criteria

The general criteria for U19 multiproject cooperative agreement applications are presented in the NIAID BROCHURE. In addition, applicants are expected to address the requirements outlined in the section, "SPECIAL REQUIREMENTS." Additional review criteria specific to this RFA are:

- o the scientific and clinical expertise and experience of the Principal Investigator, Project Leaders, and key project personnel;
- o a strong commitment to the clinical and basic study of multiple autoimmune diseases by the investigators and their institutions;
- o willingness to work cooperatively and collaboratively both within the proposed Center and with other Centers and to accept the participation and assistance of the NIAID staff in accordance with the guidelines outlined under "Terms and Conditions of Award: NIAID Staff Responsibilities"

As part of the scientific and technical merit evaluation of the research plan, reviewers will be instructed to address:

- o Adequacy of plans for including children as appropriate for the scientific goals of the research, or justification for exclusion.

AWARD CRITERIA

Funding decisions will be made on the basis of scientific and technical merit as determined by peer review, program balance, and the availability of funds.

INQUIRIES

Written and telephone inquiries concerning this RFA are encouraged. The opportunity to clarify any issues or questions from potential applicants is welcome.

Requests for the NIAID brochure "INSTRUCTIONS FOR APPLICATIONS FOR MULTI-PROJECT AWARDS" as well as inquiries regarding programmatic issues, may be directed to:

Elaine Collier, M.D.

Division of Allergy, Immunology, and Transplantation

National Institute of Allergy and Infectious Diseases

6003 Executive Boulevard, Room 4A20

Bethesda, MD 20892-7640

Telephone: (301) 496-7104

FAX: (301) 402-2571

Email: ec5x@nih.gov

Joan T. Harmon, Ph.D.

Diabetes Research Section

National Institute of Diabetes and Digestive and Kidney Diseases

45 Center Drive, MSC 6600

Bethesda, MD 20892-6600

Telephone: (301) 594-8808

FAX: (301) 480-3503

Email: JOAN_HARMON@NIH.GOV

Susana Serrate-Sztejn, M.D.

Arthritis Branch

National Institute of Arthritis, Musculoskeletal and Skin Diseases

Natcher Building, Room 5AS37G

Telephone: (301) 594-5032

FAX: (301) 480-4543

Email: szteins@ep.niams.nih.gov

Direct inquiries regarding preparation of the application and review issues, address the letter of intent to, and mail two copies of the application and all five sets of appendices to:

Kevin M. Callahan, Ph.D.

Division of Extramural Activities

National Institute of Allergy and Infectious Diseases

6003 Executive Boulevard, Room 4C20

Bethesda, MD 20892-7610
Telephone: (301) 496-8424
FAX: (301) 402-2638
Email: kc92t@nih.gov

Direct inquiries regarding fiscal matters to:

Ms. Lesia A. Norwood
Division of Extramural Activities
National Institute of Allergy and Infectious Diseases
6003 Executive Boulevard, Room 4B28
Bethesda, MD 20892-7610
Telephone: (301) 402-6581 or 496-7075
Email: ln5t@nih.gov

Linda Stecklein
Division of Extramural Activities
National Institute of Diabetes and Digestive and Kidney Diseases
Natcher Building, Room 6As-49J
Bethesda, MD 20892-6600
Telephone: (301) 594-8847
FAX: (301) 480-3504
Email: steckleinl@ep.niddk.nih.gov

Ms. Carol Fitzpatrick
Grants Management Branch
National Institute of Arthritis and Musculoskeletal and Skin Diseases
Natcher Building, Room 5AS43K
Telephone: (301) 594-3506
FAX: (301) 480-4543
Email: fitzpatric@ep.niams.nih.gov

Schedule

Letter of Intent Receipt Date: December 8, 1998
Application Receipt Date: January 8, 1999
Scientific Review Date: May 1, 1999

Advisory Council Date: May 24, 1999
Earliest Date of Award: August 1999

AUTHORITY AND REGULATIONS

This program is described in the Catalog of Federal Domestic Assistance Nos. 93.855, 93.847, and 93.846. Awards are made under authorization of the Public Health Service Act, Sec. 301 (c), Public Law 78-410, as amended. Awards will be administered under PHS grants policies and Federal Regulations 42 CFR Part 52 and 45 CFR Part 74. This program is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems review.

The PHS strongly encourages all grant and contract recipients to provide a smoke-free workplace and promote the non-use of all tobacco products. In addition, Public Law 103-227, the Pro-Children Act of 1994, prohibits smoking in certain facilities (or in some cases, any portion of a facility) in which regular or routine education, library, day care, health care or early childhood development services are provided to children. This is consistent with the PHS mission to protect and advance the physical and mental health of the American people.

[Return to Volume Index](#)

[Return to NIH Guide Main Index](#)